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Body mass index and colon cancer risk in Chinese people: Menopause as an effect modifier

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ABSTRACT

High body mass index (BMI) has consistently been associated with increased colon cancer risk in men, but not in women. It is hypothesised that menopause-related changes in oestrogen levels play a role in gender-specific risk patterns. Most studies have been conducted in Western countries, where high incidence rates are coupled with a high prevalence of obesity and relatively common use of hormone replacement therapy (HRT) in post-menopausal women. This study evaluated the correlation between body mass index (BMI) and colon cancer risk in a relatively lean population, comprising 931 cases and 1552 controls, in Shanghai, China, where HRT use was extremely rare among women, during 1990–1993. Among men, colon cancer risk significantly increased with increasing BMI (P -trend = 0.005). Among women, the risk varied with age and menopause status in a similar pattern. Within each menopause stratum, however, the BMI-related risk was similar for those aged under 55 years and those aged 55 years and over, indicating a menopause rather than age effect. Among pre-menopausal women, the odds ratios (ORs) for subjects in the highest versus lowest quintile were 1.9 (95% CI 1.1–4.9) for those under 55 years of age, and 2.2 (95% CI 1.4–8.2) for those aged 55 years and over. Among post-menopausal women, the corresponding ORs were 0.6 (95% CI 0.5–0.91) and 0.7 (95% CI 0.5–0.95), respectively. Our findings suggest that BMI predicts colon cancer risk in both genders. Among women, however, the risk is modified by menopause status, possibly through altered endogenous oestrogen levels.

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1. Introduction

A positive association of colon cancer with body mass index (BMI) has been consistently found among men, while the link is less clear among women [1–11]. The inconsistency in women may be, in part, due to variations in endogenous oestrogen levels [12–15]. The published literature indicates that, in

women, the BMI-related colon cancer risk decreases with increasing age [2,3,7,16–19]. Although most studies did not examine menopause status, the results are suggestive of a role for menopause-related alterations in hormone levels. Two recent studies have reported that the positive association between colon cancer risk and BMI was largely confined to pre-menopausal women [15,18]. Virtually all studies of

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BMI-related colon cancer risk have been conducted in Western countries, where high incidence rates of colon cancer are coupled with high prevalence of obesity and use of hormone replacement therapy (HRT) in post-menopausal women [3,7,20,21].

In general, colon cancer is uncommon in Asia [22]. In the past two decades, however, colon cancer incidence rates have been increasing sharply in Shanghai, China, which had a relative low incidence rate in the past [23,24]. The reasons for the increase are unknown, and cannot be explained fully by ascertainment criteria or increased use of screening procedures. Increasing urbanisation and Westernisation of the lifestyle in Shanghai, including physical inactivity and diet resulting in becoming overweight [25,26], may have contributed to the rising colon cancer trends. In addition, unlike most Western countries, HRT is rarely used by Chinese women [27] (in our study population, only 1.2% of women had a history of HRT). Thus, this population provides an opportunity to evaluate whether colon cancer risk increases with BMI even at levels considered within the normal range by Western standards, and whether the BMI-related colon cancer risk is modified by menopause in its natural state, that is without HRT.

2. Patients and methods

2.1. Study population

The investigation is part of a population-based case-control study of gastrointestinal cancers (pancreas, oesophagus, colon and rectum) in urban Shanghai. The study design has been described in detail elsewhere [28,29]. In brief, eligible cases were residents of the ten districts constituting urban Shanghai, aged 30–74 years, who were newly diagnosed with colon cancer (9th International Classification of Diseases codes 153.0–153.9) between October 1990 and July 1992. Cases were identified through a rapid reporting system established by the population-based Shanghai Cancer Registry. A total of 931 colon cancer cases (462 males, 469 females) were interviewed, yielding a response rate of 92%. All cases were confirmed either by histopathology (95%) or by other methods including surgical examination, computed tomography scan/ultrasound, or X-ray (5%). Excluded from the study were 59 patients who died, 14 who moved away and 7 who refused the interview.

Controls were selected randomly from residents of urban Shanghai and frequency-matched to the expected age (5-year categories) and sex distribution of the four gastrointestinal cancers combined in the overall study. Personal identification cards from the Shanghai Resident Registry were used to select controls. The cards contained information on name, address, date of birth, gender and other demographic factors. Two random numbers (a 4-digit number for locating a drawer and a 3-digit number for locating a personal identification card within the drawer) were generated to select each control. For each control chosen, an alternative control subject was also selected. If the first control could not be interviewed, the other was enrolled. A total of 1552 controls were interviewed, yielding a participation rate of 87%. Of these, 240 (15%) were alternatives.

2.2. Data collection

Study participants were interviewed in person by trained interviewers, using a structured questionnaire to elicit information on demographic and residential characteristics, diet, cigarette smoking, alcohol and other beverage consumption, medical history, family history of cancer, lifetime occupational history, and commuting and physical leisure activities. Dietary intake included 86 food items commonly consumed in Shanghai during the late 1980s. The questionnaire design was adapted from Block's food frequency questionnaire [30]. Detailed information on menses patterns, gynaecological surgery, and medication use, including HRT, were collected from female participants. Women were considered 'post-menopausal' when their menses had ceased for at least 3 months. Women with no change in menses, or with periods of amenorrhoea followed by resumption of menses and/or with change from regular to irregular menses were 'pre-menopausal.' Adult height and weight history, including usual adult weight, greatest adult weight, and weight at various age periods were collected. Analyses of BMI based on the usual adult weight are presented in this report, although similar findings were observed for BMI at various age periods. The usual BMI of each individual was calculated as usual adult weight in kilograms (kg) divided by the square of the adult height in metres (m²). Quintiles of usual BMI were determined using gender-specific cut-off points among the controls: Q1 < 19.2, Q2 19.2–20.3, Q3 20.4–21.3, Q4 21.4–22.8 and Q5 > 22.8 for men; and Q1 < 19.0, Q2 19.0–20.5, Q3 20.6–21.9, Q4 22.0–23.6 and Q5 > 23.6 (kg/m²) for women.

The study was approved by the Institutional Review Board of the Shanghai Cancer Institute, China, and the US National Cancer Institute.

2.3. Statistical analysis

Colon cancer risk was estimated by odds ratios (ORs) and 95% confidence intervals (95% CIs) using unconditional logistic regression. The lowest level of BMI was used as the reference, and risks were estimated for men and women separately. Potential confounders for the basic model were selected by means of forward-stepwise logistic regression (using $P < 0.15$ as entry criterion and $P > 0.20$ as removal criterion). Age was forced into the basic model to yield the final model. Tests for trend were performed by assessing the significance of a linear effect in median values for each category in the logistic regression model [31]. Interaction between BMI and menopause status or age was evaluated by adding an interaction term in the model. Statistical significance for interaction was assessed by the likelihood-ratio test comparing the models with and without the interaction term [32]. In addition, colon cancer risk was further examined by anatomic subsites of proximal (caecum, appendix, ascending colon, hepatic flexure, transverse colon and splenic flexure) and distal colon (descending and sigmoid colon). All ORs were adjusted for age, family history, education, monthly family income, marital status, total energy intake, and intake of red meat, carotene and fibre, and for women, number of pregnancies. Physical activity was not significantly associated with BMI in this population ($r = -0.06$). Since further adjustment for

Table 1 – Characteristics of study subjects in Shanghai, China, 1990–1993

Characteristics	Men		Women	
	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)
Total number of subjects	462 (100)	851 (100)	469 (100)	701 (100)
Age (years)				
30–49	75 (16)	130 (15)	90 (19)	108 (15)
50–59	95 (21)	182 (21)	94 (20)	194 (28)
60–64	108 (23)	195 (23)	105 (22)	147 (21)
65–69	100 (22)	183 (22)	97 (21)	136 (19)
70–74	84 (18)	161 (19)	83 (18)	116 (17)
BMI ^a				
Q1	80 (17)	171 (20)	86 (18)	139 (20)
Q2	85 (18)	168 (20)	91 (20)	131 (19)
Q3	68 (15)	169 (20)	80 (17)	147 (21)
Q4	109 (24)	170 (20)	92 (20)	139 (20)
Q5	119 (26)	169 (20)	116 (25)	139 (20)
Menopause status				
Pre-menopausal	–	–	140 (31)	153 (22)
Post-menopausal	–	–	317 (69)	534 (78)
HRT use				
Yes	–	–	3 (1)	9 (1)
No	–	–	466 (99)	692 (99)

HRT, hormone-replacement therapy; BMI, body mass index.

a Quintiles of BMI based on the gender-specific distribution of control subjects. The following cut-off points were used: Q1 < 19.2, Q2 19.2–20.3, Q3 20.4–21.3, Q4 21.4–22.8 and Q5 > 22.8 for men; and Q1 < 19.0, Q2 19.1–20.5, Q3 20.6–21.9, Q4 22.0–23.6 and Q5 > 23.6 for women.

physical activity did not alter the results significantly in either gender, it was not included in the final model. All tests were two-sided, with *P*-values of less than 0.05 considered to be statistically significant. Individuals with missing values were excluded from specific analyses. The Stata statistical package was used for all analyses (Stata Corporation, College Station, TX, United States of America (USA); release 7.0).

3. Results

Colon cancer cases and controls had comparable age distributions, but cases tended to have higher BMI than controls (Table 1). Among women, cases were more likely to be pre-

menopausal than controls. Three cases (0.6%) and 9 controls (1.3%) reported a history of HRT use.

Among men, colon cancer risk (Table 2) increased significantly with increasing BMI (*P*-trend = 0.005; OR = 1.7, 95% CI 1.1–2.4 for the highest relative to the lowest quintile of BMI), with risks comparable for men under age 55 years and those aged 55 years and over (Table 3). Among women, the overall increases in risk with BMI were only marginally significant (*P*-trend = 0.08; OR = 1.4, 95% CI 1.0–2.1 for the highest quintile) (Table 2). However, the risk patterns varied with age (Table 3); risks increased with increasing BMI among women under age 55 years (*P*-trend = 0.03) but decreased with increasing BMI among those aged 55 years and over (*P*-trend = 0.07).

Table 2 – Gender-specific risk^c for colon cancer by body mass index (BMI) among subjects in Shanghai, China, 1990–1993

BMI ^a	Men			Women		
	Case/control	OR (95% CI) ^b	<i>P</i> trend	Case/control	OR (95% CI) ^b	<i>P</i> trend
Q1	80/171	1.0 (–)		86/139	1.0 (–)	
Q2	85/168	1.0 (0.7–1.4)		91/131	1.2 (0.8–1.7)	
Q3	68/169	1.0 (0.7–1.4)		80/147	0.9 (0.6–1.3)	
Q4	109/170	1.2 (0.9–1.8)		92/139	1.1 (0.8–1.7)	
Q5	119/169	1.7 (1.1–2.4)	0.005	116/139	1.4 (1.0–2.1)	0.08

OR, odds ratio.

a Quintiles of BMI were determined based on the distribution among controls of each sex. The following cut-off points were used for BMI: Q1 < 19.2, Q2 19.2–20.3, Q3 20.4–21.3, Q4 21.4–22.8 and Q5 > 22.8 for men; and Q1 < 19.0, Q2 19.1–20.5, Q3 20.6–21.9, Q4 22.0–23.6 and Q5 > 23.6 (kg/m²) for women.

b Adjusted for age, education, family income, marital status, total energy intake, intake of red meat, carotene and fibre for both men and women; and the number of pregnancies and years of menstruation for women.

c Some numbers may not add up to the total due to missing values.

Table 3 – Risk^a for colon cancer by age and gender in Shanghai, China, 1990–1993

BMI ^b	Men ^c					Women ^c						
	Age < 55 years			≥ 55 years		Age < 55 years			≥ 55 years			
	Case/control	OR (95% CI) ^d	P trend	Case/control	OR (95% CI) ^d	P trend	Case/control	OR (95% CI) ^d	P trend	Case/control	OR (95% CI) ^d	P trend
Q1	20/53	1.0 (-)		59/116	1.0 (-)		24/59	1.0 (-)		71/84	1.0 (-)	
Q2	26/54	1.1 (0.7–2.5)		62/117	1.0 (0.6–1.5)		29/55	1.1 (0.6–2.2)		70/85	1.0 (0.5–1.5)	
Q3	21/54	0.8 (0.4–1.5)		49/113	1.1 (0.6–1.5)		29/54	1.3 (0.6–2.4)		63/83	0.9 (0.5–1.4)	
Q4	34/58	1.1 (0.9–2.9)		66/116	1.3 (0.8–2.0)		34/53	1.5 (0.7–2.6)		53/87	0.8 (0.4–1.3)	
Q5	39/56	1.6 (1.1–3.1)	0.01	84/114	1.8 (1.3–3.4)	0.008	48/53	1.9 (1.1–3.4)	0.03	48/88	0.6 (0.3–1.0)	0.07
HRT, hormone-replacement therapy; BMI, body mass index.												
a Some numbers may not add up to the total due to missing values.												
b Quintiles of BMI were determined based on the distribution among controls of each sex. The following cut-off points were used for BMI: Q1 < 19.2, Q2 19.2–20.3, Q3 20.4–21.3, Q4 21.4–22.8 and Q5 > 22.8 for men; and Q1 < 19.0, Q2 19.1–20.5, Q3 20.6–21.9, Q4 22.0–23.6 and Q5 > 23.6 (kg/m ²) for women.												
c P for interaction between age and BMI was 0.43 for men and 0.09 for women, respectively.												
d Adjusted for age, education, family income, marital status, total energy intake, intake of red meat, carotene and fibre for both men and women; and the number of pregnancies and years of menstruation for women.												

The pattern of risks when stratified by menopause status (Table 4) was similar to that stratified by age: risks increased with BMI among pre-menopausal women (P-trend = 0.01) and decreased with increasing BMI among post-menopausal women (P-trend=0.03). In order to disentangle the effect of age versus that of menopause status, we further stratified BMI-related colon cancer risk by both age and menopause status (Table 5). We found that irrespective of age (<55 years versus ≥55 years), risks significantly increased with BMI among pre-menopausal women, but decreased significantly with high BMI among post-menopausal women. Within each menopause stratum, the BMI-related risk was similar for those under age 55 years and those aged 55 years and over (OR = 1.9, 95% CI 1.1–4.9 and OR = 2.2, 95% CI 1.4–8.2, respectively for pre-menopausal women, and OR = 0.6, 95% CI 0.5–0.91 and OR = 0.7, 95% CI 0.5–0.95, respectively, for post-menopausal women).

The results did not vary meaningfully when stratified by colon subsite for both genders (data not shown). Analyses using World Health Organization (WHO) standard cut-off points for overweight and obesity yielded similar findings. The evaluations on weight changes over various age periods did not reveal consistent patterns with respect to colon cancer risk. In addition, exclusion of the 12 women who reported a history of HRT did not alter the findings in women overall and specifically among post-menopausal women.

4. Discussion

This study shows that colon cancer risks increase with increasing BMI in a relatively lean population by Western standards (the cut-off points for the highest quintile of 22.8 for men and 23.7 for women among controls in this study are well below levels considered as overweight (BMI ≥ 25) and obese (BMI ≥ 30) by the WHO standard [33]. The BMI-related colon cancer risk in this study did not vary with age among men. In women, the increases in risk were confined to younger women; among women aged 55 years or over, risks appeared to decline with increasing BMI. This apparent age effect, however, was explained largely by menopause status. Risks increased with increasing BMI among pre-menopausal women of both age groups and declined with increasing BMI among post-menopausal women of both age groups.

Our findings of increased risks of colon cancer in men and pre-menopausal women are consistent with previous studies conducted in Western countries [1–11]. Given the same level of BMI, Asians tend to have a higher percentage of body fat [34] and a larger amount of visceral fat [34], which is suggested to play a more important role in the insulin resistance syndrome than BMI per se [35,36]. It has been shown that Chinese women with BMI of only 21.2 kg/m², which is considered optimal by US standards [37], have 32% of body fat, which is considered obese by the WHO [33]. Furthermore, in this relatively lean population, higher BMI (>23) was clearly associated with an increasing prevalence of obesity co-morbidities, including diabetes and metabolic syndrome [25], which are closely associated with obesity-related hyper-insulinaemia [38–40]. Taken together, these may explain, at least in part, the increases in colon cancer risk even with relatively small

Table 4 – Risk^a for colon cancer by body mass index (BMI) and menopause status^b among women in Shanghai, China, 1990–1993

BMI ^c	Menopause status ^d					
	Pre-menopausal women			Post-menopausal women		
	Case/control	OR (95% CI) ^d	P trend	Case/control	OR (95% CI) ^d	P trend
Q1	15/32	1.0 (–)		66/96	1.0 (–)	
Q2	19/31	1.2 (0.6–2.8)		72/109	1.1 (0.6–1.5)	
Q3	20/31	1.2 (0.3–3.1)		58/110	0.8 (0.5–1.2)	
Q4	24/30	1.3 (0.6–3.2)		71/109	0.8 (0.6–1.4)	
Q5	62/29	2.9 (1.7–8.6)	0.01	50/110	0.6 (0.3–0.9)	0.03

OR, odds ratio.

a Some numbers may not add up to the total due to missing values.

b $P = 0.003$ for interaction between menopause status and BMI for colon cancer risk.

c Quintiles of BMI were determined based on the distribution among controls. The following cut-off points were used for BMI: Q1 < 19.0, Q2 19.1–20.5, Q3 20.6–21.9, Q4 22.0–23.6 and Q5 > 23.6 (kg/m²).

d Adjusted for age, education, family income, marital status, total energy intake, intake of red meat, carotene, fibre, number of pregnancies and years of menstruation.

excesses in BMI among our study population although the biological explanations for this finding could be more complex.

To date, BMI has not been consistently linked to colon cancer risk among post-menopausal western women [2,7,15,18,41]. Among HRT users, increased risks with increasing BMI were observed [15,41]. Among non-HRT users, however, observations of both positive [41] and inverse [15] associations with BMI have been reported, although only the former [41] was statistically significant. In addition, a statistically non-significant reduction in risk among post-menopausal women was found with adjustment for HRT use [18]. These inconsistent observations suggest a complex relationship between obesity, menopause-related changes in oestrogen levels, and colon cancer risk [14]. Oestrogen use has been linked with reduced colon cancer risk [42], but the exact mechanisms are unclear. It has been speculated that oestrogens may reduce colon cancer risk by decreasing bile acid production which reduces chronic irritation on the colonic mucosa [43], inhibiting cell proliferation, influencing microsatellite instability [44] and increasing the expression of vitamin D receptors (VD-R) [45]. In post-menopausal women, the

primary sources of oestrogens are adipose tissue and HRT use. In our relatively lean population of post-menopausal women who rarely used HRT, the increases in oestrogens with increasing BMI might outweigh the relative increases in deleterious effects of elevated BMI, such as increased insulin resistance, whereas in pre-menopausal women, effects of the small increases in oestrogens due to elevated BMI may be negligible relative to the large amount of oestrogens produced in the ovaries.

It could be surmised that adipose-derived oestrogens should also reduce the risk of colon cancer among obese men. However, an elevated risk has been consistently observed in men with excess BMI in previous studies. Men are more likely to have intra-abdominal obesity, which has a stronger link with increased insulin resistance than BMI per se [35,36]. In addition, it has been suggested that androgen may also up-regulate insulin-like growth factor 1R (IGF-1R) and insulin receptor substrate 1 (IRS-1) levels [15,35]. Therefore, the adverse effects from both intra-abdominal obesity and androgen in obese men may outweigh the beneficial effect of oestrogens on colon cancer development. As with oestrogen levels in women, androgen levels in men also decline

Table 5 – Risk^a for colon cancer by body mass index (BMI) and menopause status among in Shanghai, China, 1990–1993

BMI ^b	Menopause status and age							
	Pre-menopausal				Post-menopausal			
	Pre-menopausal and age < 55 years		Pre-menopausal and age ≥ 55 years		Post-menopausal and age < 55 years		Post-menopausal and age ≥ 55 years	
	Case/control	OR (95% CI) ^c	Case/control	OR (95% CI) ^c	Case/control	OR (95% CI) ^c	Case/control	OR (95% CI) ^c
Low	41/24	1.0 (–)	13/51	1.0 (–)	40/120	1.0 (–)	132/150	1.0 (–)
High	58/21	1.9 (1.1–4.9)	28/57	2.2 (1.4–8.2)	25/109	0.6 (0.5–0.91)	120/155	0.7 (0.5–0.95)

OR, odds ratio.

a Some numbers may not add up to the total due to missing values.

b Low BMI: <21.4 kg/m²; high BMI: ≥21.4 kg/m².

c Adjusted for age, education, family income, marital status, total energy intake, intake of red meat, carotene, fibre, number of pregnancies and years of menstruation.

with age. However, compared with women, the decline is less dramatic and occurs at a later age with less inter-individual variability [15]. Finally, sex hormone-binding globulin has been shown to increase with age largely among men, but not among women, thus substantially reducing available hormones in men, including the already small amount of adipose-derived oestrogens that might have been protective of colon cancer [46,47].

Several strengths of this population-based study should be noted: the high participation rate in both cases and controls minimises selection bias. The large study size permits detailed evaluation of effect modifications between BMI, menopause and age. However, the findings should be interpreted in light of a few limitations: BMI, as a measurement of overweight, varies between different ethnic groups that differ in body composition. The results, thus, may not be applicable to other populations. The lack of information on central adiposity also hindered more detailed investigation. Selective recall was unlikely to be a major problem because overweight was not a general concern and was not known to be a risk factor for colon cancer in our study population. Our study did not collect information on aspirin or other non-steroidal anti-inflammatory drug (NSAID) use, a known protective factor for colon cancer [48]. Confounding by aspirin/NSAID use or other unknown factors is possible, but unlikely, since such factors would have to be strongly related to both colon cancer and BMI in a dose-response manner.

In summary, the findings of this study in a Chinese population show that colon cancer risk increases with BMI even at levels considered within the normal range by Western standards, and support the hypothesis that menopause status is a strong effect modifier of BMI-related colon cancer risk in women, possibly due to altered endogenous oestrogen levels. These results suggest that the balance between beneficial and adverse effects of oestrogens derived from various sources may play an important role in colon carcinogenesis. The observation of reduced risk of colon cancer with increasing BMI among post-menopausal women needs further evaluation.

Conflict of interest statement

None declared.

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